NICE National Institute for Health and Care Excellence

Teduglutide for treating short bowel syndrome [ID3937]

Lead team presentation

1st Appraisal Committee A meeting
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Key clinical issues

- What would teduglutide contribute to the management of this condition, for adults and children?
  - Would it enable some people to stop or to reduce the frequency of PS?
  - Would there be a potential benefit for carers?
- When would teduglutide be initiated?
  - Would treatment be lifelong?
- Are results of the key clinical trial (STEPS) generalisable to the NHS?

Abbreviations: CKD: chronic kidney disease; IFALD: intestinal failure associated liver disease; PS: parenteral support

Background and decision problem

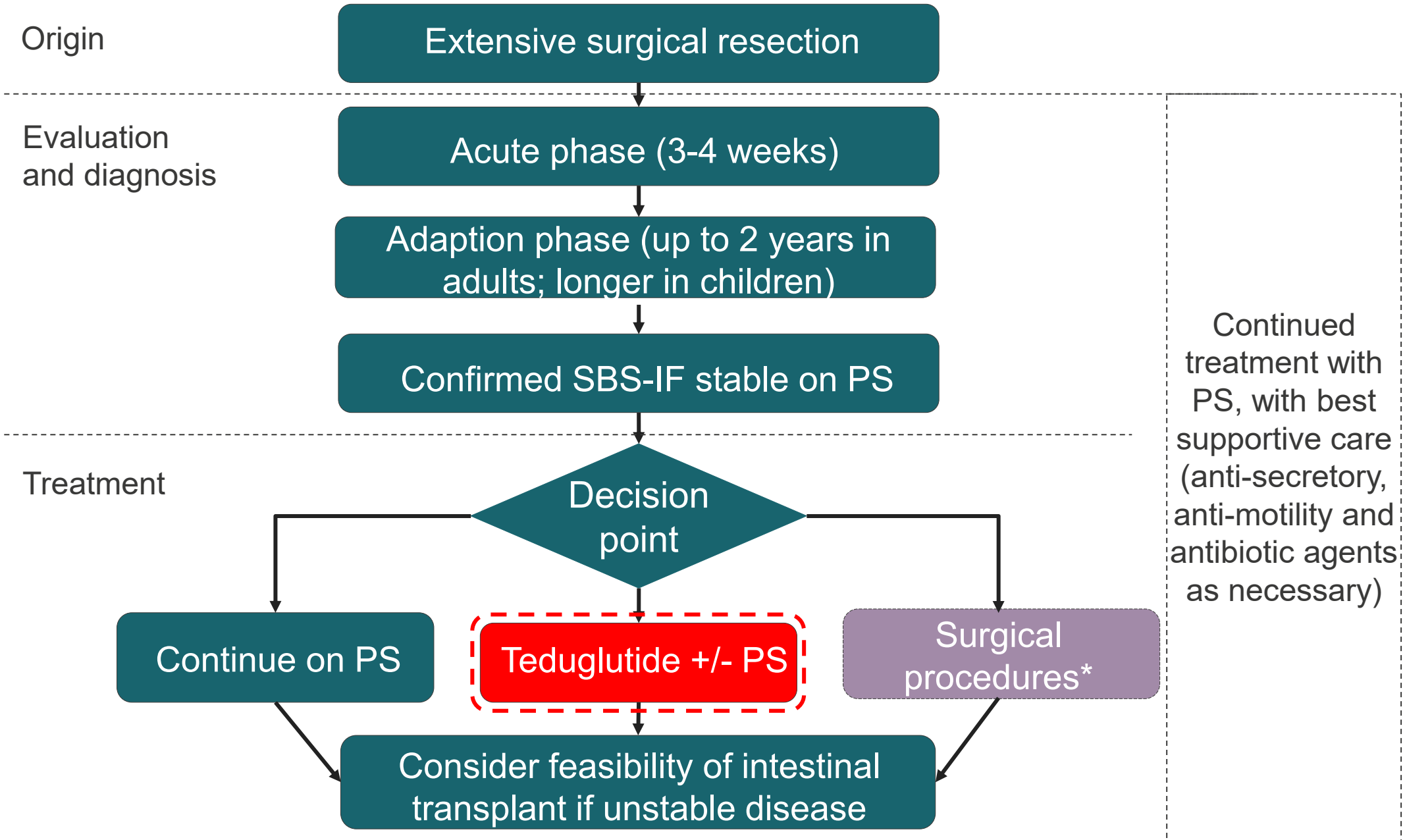
Disease background

- **Short bowel syndrome (SBS)** is most commonly caused by surgery which has been needed to remove abnormal small bowel
  - As a result of Crohn's disease or loss of blood supply to the bowel.
  - Some children can be born with a short bowel or can develop it after surgery for life threatening bowel problems
- Intestinal failure can be classified as type 1, 2 or 3. The company submission focuses only on patients with stable PS needs (type 3).
- Type 3 intestinal failure[2] (SBS-IF) is a **chronic** and potentially **life-threatening** condition characterised by reduced absorption of nutrients, water and electrolytes.
- Paediatric type 3 SBS-IF is also chronic and potentially life-threatening.
  - Symptoms include malnutrition, dehydration, and metabolic and electrolyte disturbances.
- Treatment is **parenteral support** (PS) and an estimated **500** adults in England with short bowel syndrome are dependent on long-term PS.[1]
  - intravenous delivery of nutrients and fluids, for an average of 10-14 hours overnight 2-7 days per week.
  - Majority of people self-administer at home, using a permanent intravenous tube. Places a **huge burden** on patients as they are attached to an infusion pump for long periods of time.
- Long term use of PS itself is associated with **life threatening complications** such as blood infections, blood clots, and kidney and liver failure.

[1]British Artificial Nutrition Survey report. 2016

[2]Type 3: long-term intestinal failure; usually stable people who are able to be managed at home with home-based parenteral nutrition

Treatment pathway- SBS-IF



Qn. At what stage would teduglutide be initiated?

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*Surgery is not a relevant comparator as they are rarely performed in practice

Source: Company submission, doc B, figure 4. PS, parenteral support; SBS-IF, short bowel syndrome with type 3 intestinal failure.

Patient and carer perspectives (PINNT; Short Bowel Survivor and Friends)

- Being diagnosed with short bowel syndrome is extremely difficult to come to terms with both for patients and their family and friends. It affects patients' mental health and day-to-day activities
- Parenteral support is lifesaving, but highly complex and its complications can be life-threatening
- There is unmet need for the reduction of time on parenteral support to increase patient's and carer's quality of life

"Living with SBS-IF is a constant round of pain and discomfort, tiredness and lethargy. Disturbed sleep affects not only the child but the whole family. "

"[Overnight stay is] too much organisation and worry, also I need a fridge large enough to take 3.5 litres parenteral support feeds."

"[he] has definitely been limited in his career due to his condition…his condition limits certain activities at the weekend and late nights are not an option"

"not only the patient who experiences disturbed sleep patterns but anyone else sharing the bedroom or even in the household"

"There is constant worry for the family about sepsis, liver failure, loss of line sites resulting in the need for bowel transplant"

"I believe he needs this 'medicine' [teduglutide] for him to have a normal functioning life"

"[Teduglutide] has not only reduced the number of nights on parenteral support but also reduced diarrhoea and vomiting and it has given me more freedom to spend time with my other child"

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Abbreviations: PINNT: Patients on Intravenous and Naso-gastric Nutrition Treatment

Clinical perspectives

- The main treatment for SBS is nutritional support, which can be given enterally or intravenously (known as parenteral support)
- People with SBS also receive drugs to promote nutrient absorption, including antimotility agents and antisecretory agents, such as proton pump inhibitors
- Teduglutide would ultimately decrease the number of people requiring PS

"Parenteral support places a huge burden on people, as they are required to be attached to an infusion pump for many hours each night, several nights a week"

"Good survival rates.. However complications do occur with infection or thrombosis associated with central venous catheters as well as IFALD"

"For the people who I did have on this treatment [teduglutide], one came off his intravenous nutrition support altogether…substantial benefit to the health economy as well as his quality-of-life"

"[Teduglutide] definitely has a place in a treatment algorithm. People who are stable would be offered this… especially helpful for people deficient of GLP-2 to correct their deficiency"

"People who only need small amounts of parenteral nutrition… have been shown to be more likely to be able to come off parenteral nutrition support as a result of this treatment [teduglutide]"

"[Teduglutide] should be restricted to be prescribed by experienced specialist centres… people can be referred to the appropriate hospital or centre"

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Abbreviations: GLP-2: human glucagon-like peptide 2; IFALD: intestinal failure associated liver disease

Teduglutide (Revestive®)

Full Marketing authorisation	The treatment of patients aged 1 year and above with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.
Stopping treatment	Marketing authorisation specifies: • **Adults**: treatment should be stopped if no overall improvement of the patient condition is achieved. Treatment effect should be evaluated after 6 months; if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered • **Children over 2 years**: treatment effect should be evaluated after 6 months • **Children below 2 years**: treatment effect should be evaluated after 12 weeks • Company model: treatment is discontinued for anyone without a reduction of at least one day off PS per week at 12 months (compared to baseline)
Dosage and administration	0.05 mg/kg*, administered by subcutaneous injection once daily
Mechanism of action	Teduglutide is a modified analogue of the naturally occurring human glucagon-like peptide 2 (GLP-2), a peptide that promotes nutrient absorption
List price	Teduglutide 5mg vial: £521.98 Teduglutide 1.25mg vial: £260.99 Patient Access Scheme (PAS) approved by NHS England.

*In adults and children with moderate and severe renal impairment (creatinine clearance less than 50 ml/min), and end-stage renal disease, the daily dose should be reduced by 50%.

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	People with short bowel syndrome who are stable following a period of intestinal adaptation after surgery	Aligned with marketing authorisation: People aged ≥1 year old with short bowel syndrome who are stable following a period of intestinal adaptation after surgery
Intervention	Teduglutide in addition to established clinical management	As per final scope
Comparators	Established clinical management without teduglutide (including parenteral support, antimotility and antisecretory agents, fluid restriction and dietary optimisation)	As per final scope
Outcomes	• reduction in parenteral support requirements (volume and frequency) • overall survival • adverse effects of treatment • health-related quality of life • impact on carers	As per final scope

Clinical effectiveness

Clinical evidence summary

Only clinical data from adults used in the model

Adults

Used in economic model

- **STEPS**: Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week trial
- **STEPS-2**: Two-year, open-label, multi-national, extension study for patients screened or treated in STEPS
- **PSP:** A non-interventional Patient Support Programme in Australia

Not used in economic model

- **STEPS-3**: Up to one year, open-label extension study for patients in STEPS-2 at 5 US sites
- **004**: Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week study
- **005**: 28-week, open-label, multi-national, extension study for patients treated with teduglutide or placebo in 004

Children and young people

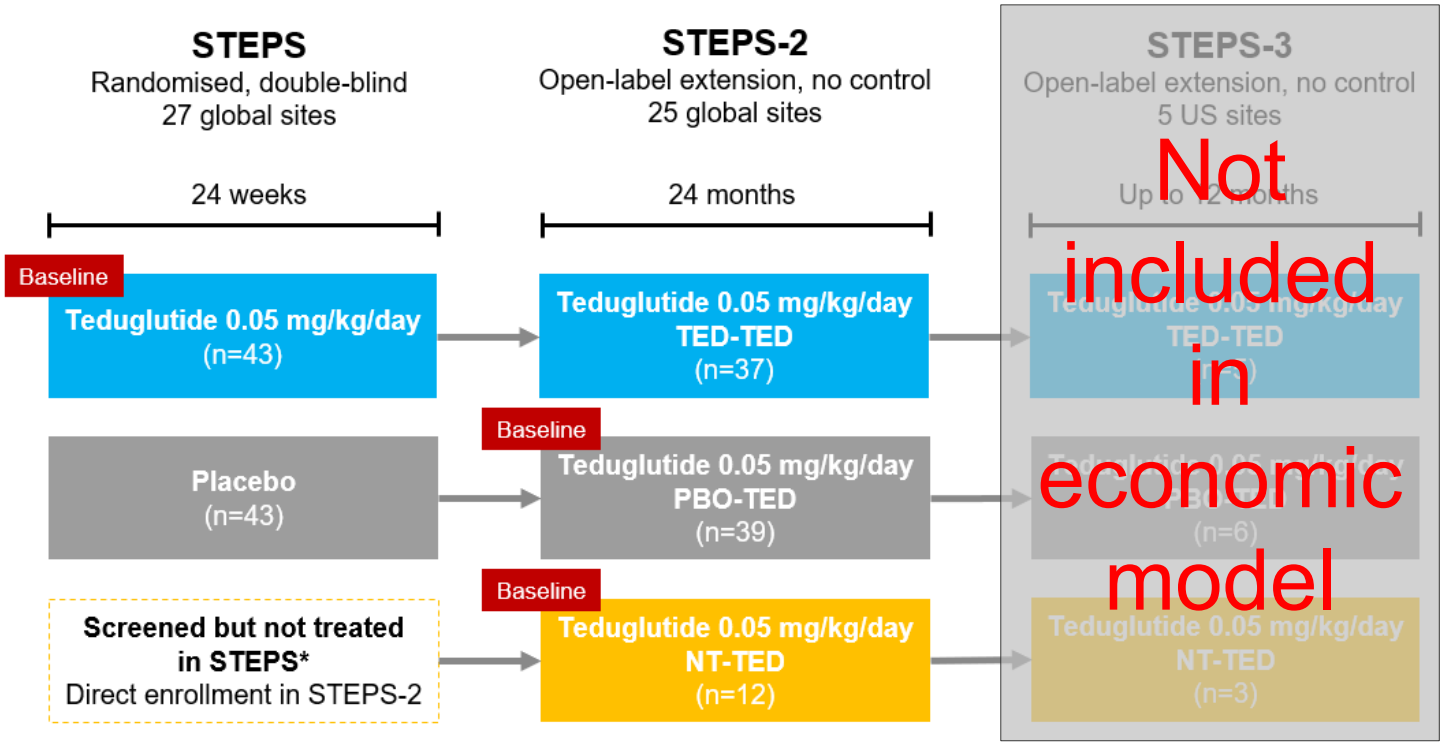
- No clinical data from paediatric studies used; small patient numbers and non-continuous treatment in follow-on studies
- Children likely benefit more than adults; increased potential for intestinal adaptation.
  - Different starting age and time horizon, paediatric-specific survival and hospital costs (specialised visits, line sepsis) used

- **C13**: Phase 3, open-label, non-randomised, 12-week study UK, US
- **SHP633-303**: Open-label, long-term extension study to C13
- **C14**: Phase 3, multi-national, open label, non-randomised, 24-week study
- **SHP633-304**: Open-label, multi-national, long-term extension to C14 and SHP633-301

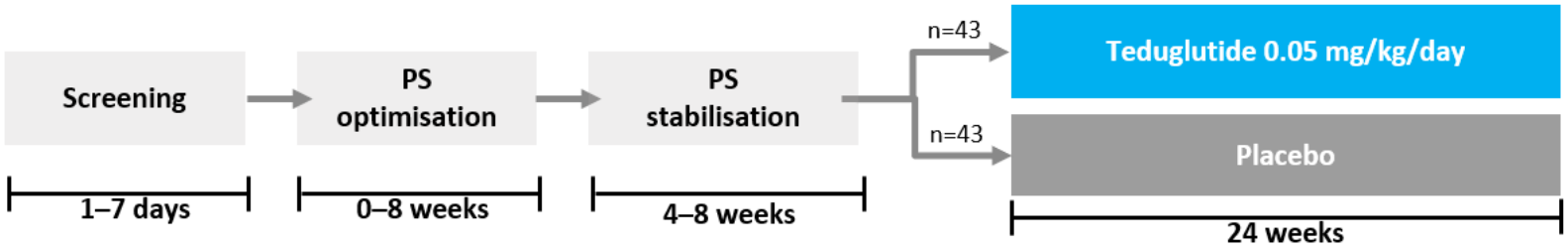
Clinical evidence (adults)

(used in economic model)

Overview of STEPS clinical programme



Overview of randomised controlled trial design for STEPS



Source: Company submissions, figures 5 and 6. **Abbreviations**: NT-TED: not treated in STEPS, teduglutide in STEPS-2, PBO-TED: placebo in STEPS, teduglutide in STEPS-2, TED-TED: treated with teduglutide in STEPS and STEPS-2; PS, parenteral support.

Clinical evidence (adults)

'Days per week of PS' outcome used in model

	STEPS	STEPS-2	Patient Support Programme
Study design	Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week trial	Two-year, open-label, multi-national, extension study for patients screened or treated in STEPS	A non-interventional Patient Support Programme (PSP)
Population	Adults (≥18 years old) with SBS-IF receiving PS for ≥3 days per week	Adults (≥18 years old) with SBS-IF screened or treated in STEPS	Real-world patients receiving teduglutide in Australia
Weaning* algorithm	PS volumes could reduce by a max of 30% baseline volume each visit	PS volumes could reduce by a max of 30% baseline volume each visit	No weaning algorithm applied, weaning according to routine clinical practice
Intervention	Teduglutide 0.05 mg/kg/day (n=43)	Teduglutide 0.05 mg/kg/day (n=88)	Teduglutide 0.05 mg/kg/day [redacted]
Comparator	Placebo (n=43)	None	None
Outcomes	• **PS Volume** (primary) • **Days per week of PS** • Safety	• **PS volume** (primary) • **Days per week of PS** • Safety	• **Days per week of PS** • Volume of PS
Location	• USA, Canada, Denmark, France, Italy, Netherlands, Poland, Spain, UK	• USA, Canada, Denmark, France, Germany, Italy, Poland, Spain, UK	• Australia

Source: company submission, table 5. **Abbreviations**: PS, parenteral support; SBS-IF, short bowel syndrome with type 3 intestinal failure
*Used to reduce the volume of PS required; condition being urine volumes during preceding 48hrs were ≥10% above baseline

STEPS trial and PSP - Baseline characteristics

STEPS and PSP are [redacted]

Baseline characteristics of studies included in economic model only

	STEPS		PSP
Characteristic	**Teduglutide (N=43)**	**Placebo (N=43)**	[redacted]
Median age, years	50.9	49.7	[redacted]
Mean days per week of PS (SD)	5.6 (1.7)	5.9 (1.5)	[redacted]
Time receiving PS at baseline, n (%)			
< 1 year	0 (0)	NR	[redacted]
≥ 1 year to < 2 years	11 (25.6)	NR	[redacted]
≥ 2 years	32 (74.4)	NR	[redacted]

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Source: ERG report, Table 7. **Abbreviations**: PS, parenteral support; PSP, patient support programme; SD, standard deviation.

Weaning for people with SBS

Company: weaning in clinical practice is more liberal than in STEPS

- Weaning = reducing parenteral support (PS) and gradually moving people onto an oral diet
  - PS reductions can involve decreasing days of PS per week or decreasing PS volume
- Weaning algorithms can be conservative (small reductions in PS allowed over time) or liberal (larger reductions in PS allowed over time)
- In STEPS, urine output determined magnitude of weaning
- **Company: PS weaning algorithm used in STEPS is more conservative than would be used in clinical practice. In the real world, PS volume reductions are often attempted earlier, more frequently and reach a larger magnitude than in STEPS**

	Weaning algorithm used in STEPS
Condition	PS volumes could be reduced if urine volumes during the preceding 48 hours were ≥10% above baseline
Magnitude	Between 10–30% of baseline PS volume at each timepoint
Timepoints at which reductions could be made	Study visits on weeks 2, 4, 8, 12, 16, 20 and 24

Source: company submission doc B, Table 13

Qn. How are people weaned in clinical practice?
Qn. Is the weaning algorithm in STEPS generalisable to the NHS?

Abbreviations: PS, parenteral support

Results from teduglutide clinical trials vs placebo in adults (STEPS): reduction in PS

Higher proportion of patients on teduglutide achieved ≥20% reduction in PS volume than placebo

	STEPS		004 (not used in model)	
	Teduglutide	Placebo	Teduglutide	Placebo
% of patients with ≥20% reduction in PS volume at week 20 sustained to week 24 (primary endpoint)	63% (n=27/43)	30% (n=13/43)	46% (n=16/35)	6% (n=1/16)
% PS volume reduction at week 24 (from baseline)	[redacted]	[redacted]	[redacted]	[redacted]
% 1-day or more reduction in weekly actual PS use at week 24 [a]	53.8% (n=21/39)	23.1% (n=9/39)	NR	NR

Qn. What is the most important outcome for people with SBS? Is it a reduction in the number of days they require PS?

[a] Among patients who completed 24 weeks of treatment (n=39 in each arm)

Source: ERG report, Table 8. **Abbreviations**: NR: not reported; PS, parenteral support

1. Generalisability of STEPS placebo response (1)

Company:

- STEPS placebo response unrealistically high due to reliance of weaning algorithm on urine output
- [redacted]
  - [redacted]
  - [redacted]
  - STEPS patients underwent 8 to 16 weeks of PS stabilisation/optimisation – any reductions in PS observed in placebo arm not attributed to further optimisation of care
- No biological reason why PS requirements should change over time for people having SoC only
- No such reductions expected for patients in routine practice with no weaning algorithms
- Weaning algorithms in STEPS/STEPS-2 underestimate reduction in PS for teduglutide; **teduglutide transition probabilities therefore estimated using pooled IPD from STEPS, STEPS-2 and PSP (004 and 005 trials rejected due to stricter, less generalisable weaning)**
- Pooled real world evidence vs STEPS and PSP as evidence for underestimation: [redacted]

Time point	Patients gaining independence from PS with teduglutide		
	STEPS	PSP	Real-world (8 studies)
6 months	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	-
12 months	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	-

Source: Company submission, figure 20. **Abbreviations**: PS: parenteral support; PSP: Patient Support Programme

1. Generalisability of STEPS placebo response (2)

ERG:

- [redacted]
- Company's explanation plausible but any ***comparison of effects between observational studies and randomised trials should be interpreted with caution***
  - no comparator treatment; prone to methodological bias, heavy censoring and no allowance for potential reversal of PS reductions
- Provided scenario that applies placebo response from STEPS to SoC arm for lifetime horizon
  - Explore if mechanisms similar to those responsible for placebo response could be responsible for reductions seen in teduglutide arm - likely overly conservative, substantial increase in ICER
- Satisfied that responses in teduglutide arms of STEPS study is sustainable, less sure of PSP data

Clinical experts

- May be possible to reduce PS for short period of time; not sustainable if medical advice followed
- Weight loss observed in SoC arm; suggests SoC 'pushed themselves too hard' to reduce PS
- However, weight **gain** in teduglutide group suggests they were given too much PS, and might have been able to wean more rapidly as a result

Q: Do people with short bowel syndrome experience any sustainable reduction in parenteral support (PS) with current standard of care (that is, in the absence of teduglutide treatment)?
Q: Is it feasible that 23% of people in the placebo arm of STEPS have reduced their number of days with PS? Is this generalisable to the NHS?

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Abbreviations: PS: parenteral support; PSP: Patient Support Programme; SoC: standard of care

Results from teduglutide clinical trials (STEPS): survival and quality of life

Survival

- Only 3 deaths occurred during STEPS and STEPS-2; unable to use to model long term survival in patients with SBS-IF

Health related quality of life

- **Quality of life data comparing teduglutide and placebo captured in STEPS**
  - SBS-QoL used to measure QoL, asked to rate influence of disease on 17 items, including general wellbeing, leisure activities, working life and social life
  - Did not demonstrate statistically significant QoL differences between teduglutide and placebo groups after 24 weeks of treatment
  - [redacted]

Group	Reduction (improvement) in mean SBS-QoL score	Mean difference
Teduglutide	-11.7 (SD 26.8)	-5.4 in favour of teduglutide (p=0.407)
Placebo	-6.3 (SD 30.5)	

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Source: company submission, section B.2.6.3. **Abbreviations**: PS, parenteral support; QoL: quality of life

Clinical trial evidence (children and young people)

Company used data from adults in its paediatric model instead of data from its trials in children and young people

	C13	SHP633-303	C14	SHP633-304
Study design	Phase 3, open-label, non-randomised, 12-week study UK, US	Open-label, long-term extension study to C13	Phase 3, multi-national, open label, non-randomised, 24-week study	Open-label, multi-national, long-term extension to C14 and SHP633-301
Comparator	Placebo (PS; n=5)	None	Placebo (PS; n=9)	None
Primary endpoint	Reduction in PS days per week at 12wk	[redacted]	% achieving a clinical response, (≥20% reduction in PS volume at 24wk)	[redacted]
Results	[redacted]	[redacted]	Teduglutide 0.05 mg/kg/day: **69% (n=18/26)**; placebo: 11% (n=1/11)	[redacted]
Rationale for exclusion	C14, C13 included small number receiving teduglutide; SHP633-304, -303 allowed non-continuous teduglutide treatment. Adult data do not have these issues, children likely derive more benefit from teduglutide, justified to model with adult data			

Qn. Why were data from children and young people not used in the modelling?

*Study protocol suggested a weaning algorithm but it was at the discretion of the investigator.

Source: company submission, table 6. **Abbreviations**: PS, parenteral support; SBS-IF, short bowel syndrome with type 3 intestinal failure

Clinical evidence – pooled safety for adults

Frequency and severity of adverse events broadly similar between teduglutide and placebo except abdominal distension

Adverse event grouping† or adverse event preferred term occurring in at least 5% of patients in teduglutide RCT + extension group, n (%)	Teduglutide group, RCT + extensions (STEPS, STEPS-2, 004, 005)	Teduglutide group, RCTs (STEPS + 004) only	Placebo group, RCTs (STEPS + 004) only
Gastrointestinal stoma complications‡	31 (45.6)	17 (37.8)	3 (13.6)
Abdominal pain†	72 (41.6)	42 (38.5)	16 (27.1)
Upper respiratory tract infection†	50 (28.9)	30 (27.5)	8 (13.6)
Catheter sepsis events†	47 (27.2)	17 (15.6)	10 (16.9)
Abdominal distension	32 (18.5)	18 (16.5)	1 (1.7)

†Preferred terms in AE groupings represent medically similar terms.

‡Percentages calculated based on number of patients with stoma (n = 45 for RCT teduglutide group; n = 68 for RCT/ extension teduglutide group; n = 22 for RCT placebo group). **Source**: Company submission, Table 20

Clinical evidence – pooled safety for children and young people

Safety profile is similar to that observed in the adult population

Adverse events occurring in at least 5% of patients (pooled data from C13, SHP633-303, C14 and SHP633-304)	Children and young people receiving teduglutide (N=89)
Vomiting	46 (51.7)
Pyrexia	39 (43.8)
Upper respiratory tract infection	37 (41.6)
Cough	30 (33.7)
Device-related infection*	26 (29.2)
Abdominal pain	23 (25.8)
Diarrhoea	23 (25.8)
Headache	18 (20.2)
Nasopharyngitis	18 (20.2)
Viral infection	18 (20.2)

Source: Company submission, Table 21

Cost-effectiveness

Key cost effectiveness issues

Cost of home parenteral nutrition has greatest effect on ICER

Issue		Description / key questions	Impact on the ICER
1. ICER for children vs adults		Cost effectiveness for children is much more favourable than for adults: what are the reasons for this?	N/A
2. costs + resource use: HPN + associated medicines	**a**	What is the most appropriate price to use for HPN? • Large differences in the prices by provider • **Major impact on the ICER** • Ranging from cost saving to >£40,000/QALY* • Prices are confidential – full impact seen in Part 2 only	
	b	Associated medicines • What are the most appropriate dosing and administration assumptions for PPIs and antimotility agents in adults and children, including those who are PS independent? • Are they given orally or intravenously? • What are the most appropriate dosing and administration assumptions for ondansentron, fragmin and Taurolock in adults and children?	

Key:
Model driver; Unknown impact; Small/moderate impact

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Abbreviations: HPN, home parenteral nutrition; PPI, proton pump inhibitor, * ERG base case. HPN cost includes delivery and nursing costs

Other cost effectiveness issues

Issue	Description / key questions	Impact on the ICER
3. Health state utility by frequency of PS	Are the company's utilities representative of quality of life for people who have reduced the number of days on PS?	
4. Modelling of overall survival in adults	Are the survival extrapolations plausible and appropriate?	
5. Modelling of complications (IFALD and CKD)	Is the company's approach to modelling IFALD and CKD appropriate?	
6. Modelling of adverse events	Is it reasonable to assume adverse event rates diminish over time and improve over standard care?	
7. Costs related to line sepsis	Does the incidence of line sepsis increase with the number of days on PS?	

Key:
 Model driver;  Unknown impact;  Small/moderate impact

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Abbreviations: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; PS, parenteral support.

How does teduglutide affect costs and QALYs in the model?

- Teduglutide is modelled to affect both costs and QALYs:

Costs	QALYs

• Increases drug treatment acquisition and monitoring costs
• Reduces costs associated with PS
• Reduces costs associated with complications associated with PS frequency
• Changes adverse events compared with standard of care (SoC)
  • SoC: STEPS AE rates (0-6m) for entire time horizon
  • Teduglutide: STEPS AE rates for first 6 months, then STEPS-2 AE rates for remaining time horizon
	• Reduces the number of days that people require PS per week – modelled to improves the health-related quality of life of patients and carers
	• Reduces the incidence of complications associated with the frequency of PS use
	• Changes the incidence of other adverse events compared to standard of care

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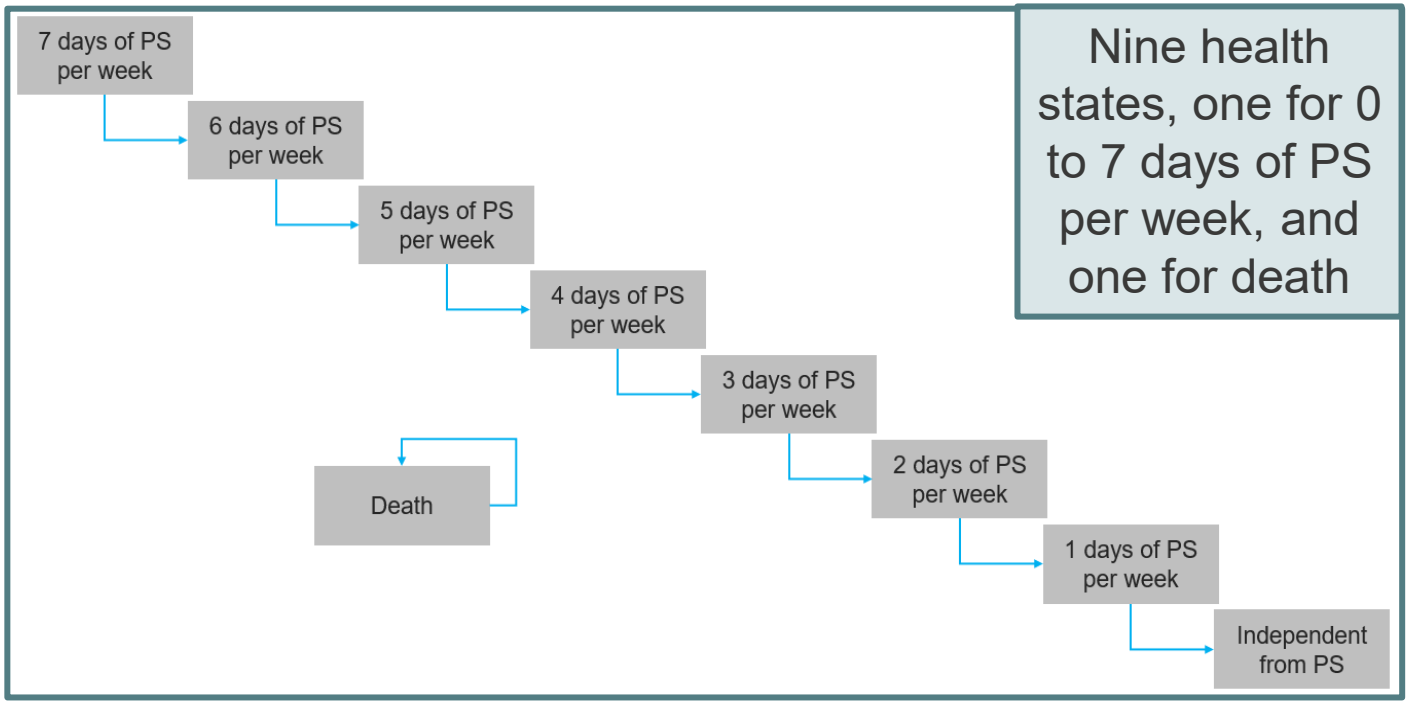
Source: ERG report, section 1.2, page xiv.
Abbreviations: AE: adverse event; PS, parenteral support; QALYs, quality-adjusted life-years; SoC: standard of care

Company's model (1)

Economic model structure



- Model structure selected as number of days per week of PS is most relevant outcome
- Distribution between health states at start is equal between arms, determined by baseline days of PS required by people enrolled in STEPS and PSP
  - Assumed PS needs of patients receiving standard of care doesn't change over time
  - People on teduglutide can either reduce PS requirement by a maximum of 1 day per 28-day cycle, or remain stable
    - **ERG:** above may be a simplifying assumption from a clinical standpoint, but model structure agreeable due to complexities of modelling such a heterogeneous disease

Source: Company submission, figure 21, ERG report section 4.2.2. **Abbreviations:** PS: parenteral support

Company's model (2)

Base case	Adult (aged ≥18 years)	Paediatric (aged 1–17 years)
Model type	Markov structure, with health states defined by the number of days per week that patients are required to receive parenteral support (PS), as well as whether patients are alive or dead	
Population	Patients with SBS-IF who are stable following a period of intestinal adaptation after surgery.	
Starting age	50 years old	6 years old
Intervention	Teduglutide 0.05 mg/kg/day	
Comparator	Standard of care: parenteral support, antimotility and antisecretory agents, fluid restriction and dietary optimisation	
Treatment effect	People receiving standard care do not move between number of PS days (health states); teduglutide transition probabilities calculated using pooled individual patient data from the STEPS and STEPS-2 trials together with data from the PSP	
Time horizon	50 years	94 years
Model cycle	4-weekly	
Discount rates	3.5% for both health and cost outcomes	
Utility values	Ballinger 2018 - UK general population vignette study using time-trade off	
Costs	NHS reference costs 2019/2020; BNF; PSSRU	
Perspective	NHS and Personal Social Services	

Source: Company submission, Section B.3.2 and Table 23. **Abbreviations**: BNF: British National Formulary, PSSRU: Personal Social Services Research Unit.

Summary of company and ERG base cases[a] (1)

Company and ERG have different opinions on associated medications

Issue	Company base case assumption	ERG base case assumption	Available scenarios
2a. Cost of PS to be discussed in confidential Part 2 of meeting			
2b. Associated medications – resource use and costs [b]			
PPIs	80 mg daily by IV	• Adult: 80 mg daily orally • Paediatric: 50% receive PPIs IV at 40 mg	• 40 mg per day (oral) • Varying percentages of PS independent people continuing with PPIs
Antimotility agents	• 32 mg loperamide orally daily • 240 mg codeine phosphate IV daily	• Adult: codeine costed as oral • Paediatric: 16 mg loperamide, no codeine	• Varying percentages of PS independent people continuing with antimotility agents
Fragmin	5,000 units daily	• Adults: as per company • Paediatric: None	–
Ondansentron	16 mg daily solution for injection	• Adults: as per company • Paediatric: None	• Removed • 12 mg per day (IV) • Given orally
Taurolock	Everyone gets daily Taurolock		50% get daily Taurolock
Prescribing	Concomitant medications prescribed in primary care		Secondary care

[a]Assumptions apply to adult and paediatric populations unless otherwise stated; [b]PS independent people do not receive these medications, they only attend follow-up visits. **Abbreviations:** IV: intravenous; PPI: proton pump inhibitors; PS: parenteral support.

Summary of company and ERG base cases[a] (2)

Company and ERG aligned on other issues

Issue	Company base case assumption	ERG base case assumption	Available scenarios
3. Health state utilities	Utilities obtained from health state vignettes instead of STEPS		• Reduce range of health state utilities by different percentages
4. Modelling of overall survival in adults	Log-normal		• Exponential • Increase in mortality risk vs general population • Adjust mortality hazard for PS independent people against disease specific mortality
5. Modelling of complications (IFALD and CKD)	Expected cumulative proportions by PS health state - teduglutide reduces by reducing PS frequency		• No complications
6. Modelling of adverse events	Teduglutide arm uses STEPS (teduglutide data) and STEPS-2 (teduglutide data). Standard care uses placebo arm from STEPS.		• Equalise post-6-mo AE rates in teduglutide arm to standard care arm • Equalise post-6-mo AE to pre-6-mo AEs in teduglutide arm (just using STEPS)
7. Health state costs (line sepsis)	• Equal number of specialist visits regardless of PS independence • Incidence of line sepsis increases with increasing frequency of PS		• Assume flat rate of line sepsis across the PS health states

[a]Assumptions apply to both adult and paediatric populations unless otherwise stated.

Abbreviations: AE: adverse event; PS: parenteral support; PSP: Patient Support Programme

1. Difference in ICERs for children vs adults

ICERs for children much more favourable than for adults

- Assumptions and data sources very similar between the model for adults and the model for children and young people. The only differences are:

	Adults	Children and young people
Starting age (years)	50	6
Time horizon (years)	50	94
Source of survival data	Salazar et al.	Pironi et al.
Hospital costs for specialised visits and line sepsis	Shorter hospital stays and less frequent hospitalisation	Longer hospital stays and more frequent hospitalisation (line fracture occlusion only) 4 specialist visits a year, with additional tests*
Dosing	5mg teduglutide	1.25mg teduglutide until 8yrs
Carer assumptions	One carer	Two carers; utility decrements of carers double that of adults

Note, in paediatric model, children and young people are assumed to switch to adults assumptions when they reach age 18yrs.

ERG

- Adult and paediatric models similar – disparity between ICERs due to starting age and time horizon
- QALY and cost benefits have longer to accrue in the paediatric model

Abbreviations: ICER, incremental cost-effectiveness ratio. *haematology, inflammatory markers, clinical biochemistry

2b. Parenteral support and associated medications (1)

Company and ERG have different assumptions relating to PPIs and antimotility agents

	Company base case		ERG base case		ERG Comment	Clinical expert comment
Item	**Adults**	**Paediatric**	**Adults**	**Paediatric**		
PPIs: omeprazole / pantoprazole	80 mg IV		80 mg **orally**	**50% do not receive PPIs, 50% get 40 mg IV**	IV doses reasonable, consistent with oral doses (exc. fragmin). Change to oral lowers costs	Can be given orally in adults, given by IV in ~50% of children
Antimotility agent: loperamide	32 mg orally		As per company	**16 mg**	Company doses reasonable but usually given orally	Can be given orally in adults, lower doses (by body weight) in children
Antimotility: codeine	240 mg IV		240 mg **orally**	**None**		Not used in children

- All doses given daily while on PS. Company and ERG assume treatment stops when off PS
- Differences between ERG and company base cases **highlighted in red**

Q. Are the company's or ERG's assumptions most appropriate?
Q. Are PPIs given orally or intravenously?
Q. Should their use be modelled differently for adults vs children?

Abbreviations: IV, intravenous; PPI: proton pump inhibitors; PS: parenteral support.

2b. Parenteral support and associated medications (2)

Company and ERG have different assumptions relating to fragmin, ondansentron and Taurolock

	Company base case		ERG base case		ERG Comment	Clinical expert comment
Item	**Adults**	**Paediatric**	**Adults**	**Paediatric**		
Fragmin	5,000 units daily		As per company	**None**	–	Not used in all patients
Ondansetron	16 mg daily solution for injection		As per company	**None**	Expert does not see ondansetron use in practice. Dose consistent with oral dose	Not used in children
Taurolock	Daily		As per company		Expert validated daily Taurolock	Use is dependent on patient severity, only used in ~50% of children

- All doses given daily while on PS. Company and ERG assume treatment stops when off PS
- Differences between ERG and company base cases **highlighted in red**

Q. Are the company's or ERG's assumptions most appropriate?
Q. Are fragmin, ondansentron and Taurolock given daily in all people on PS?
Q. Should their use be modelled differently for adults vs children?

Abbreviations: IV, intravenous; PPI: proton pump inhibitors; PS: parenteral support.

2b. Parenteral support and associated medications (3)

Other issues

- Company and ERG assume all associated medications (PPIs, antimotility agents, fragmin, ondansentron and Taurolock) are given daily while people are having PS, and treatment is stopped if people are weaned off PS
- **Moderate to high impact if committee accept company's administration assumptions, very small impact in ERG preferred base case**

Q. Is this appropriate? Or does treatment continue when people are weaned off PS?

- Whether medications are prescribed in primary or secondary care affects the source of costs:
  - Primary care: use drug tariff price from BNF (company and ERG base case)
  - Secondary care: use eMIT and confidential CMU prices (ERG scenario analysis)
- ERG expert advised medications would be provided through repeat prescriptions by the GP

Q. Are associated medications prescribed in primary or secondary care?

Abbreviations: IV, intravenous; PPI: proton pump inhibitors; PS: parenteral support.

3. Health state utility by frequency of parenteral support

Company

- Reduction in parenteral support (PS) days is most relevant outcome of teduglutide treatment when considering impact on quality of life of patients/carers; backed by patient and clinical experts
- Quality of life data collected in STEPS fails to show significant effect of treatment and indicates inconsistent relationship between PS days and health state utility (highest utility observed at 4 days of PS per week) - lacks face validity
- Uses values obtained for health state vignettes instead of trial; Ballinger et al: company base case
- Carer utilities are assumed to be related to PS days in model

ERG

- Accepts the company's use of the vignette utilities but has explored uncertainty in scenario analyses
- Company's approach may exaggerate quality of life benefit of PS reductions
- Carer utilities derived from UK caregiver survey do not provide support for association between PS days and carer health-related quality of life

Clinical and patient experts

- Unanimous agreement that reduction in PS days is of huge benefit to patients and carers
- Reduction in nights of PS in children would have multiple effects on both the child and their carers, including more relaxed and flexible lifestyle and participation in activities
- Improved energy levels for both carers and child, more alert during the day for work/school
  - Less PS and ancillary equipment required for holidays/none required for single nights away

NICE

Q: Is the company's use of published vignettes instead of STEPS trial data for health state utilities appropriate?

Abbreviations: PS: parenteral support.

4. Modelling overall survival in adults (1)

Company

- Survival based on extrapolation of published Kaplan-Meier data for people with SBS-IF on long term PS - not influenced by health state or treatment (Salazar et al.)
- Clinical expert opinion: mortality for people on PS are linked to the underlying SBS rather than PS
- Uses log-normal curve for base case; based on statistical fit and hazard function of Salazar data
- Survival probabilities adjusted using Life Tables for England from ONS to ensure extrapolations did not cause the rate of mortality to reduce below general population
- Exponential extrapolation is a poor fit to the underlying data

ERG

- Questioned if it was plausible for a proportion of patients with SBS-IF on long-term PS to have mortality rates in line with the general population (as is assumed by company's adjustment)
- Uses log-normal extrapolation in base case – accepts that it provides better fit than exponential
- Explores exponential curve; retains mortality hazard higher than general population for longer
- Clinical expert supported that children who wean off PS can achieve normal survival outcomes; those who remain on PS experience an excess mortality risk compared to general population
  - Omission of survival benefit for teduglutide is conservative with respect to QALY gains, but may also underestimate the incremental cost

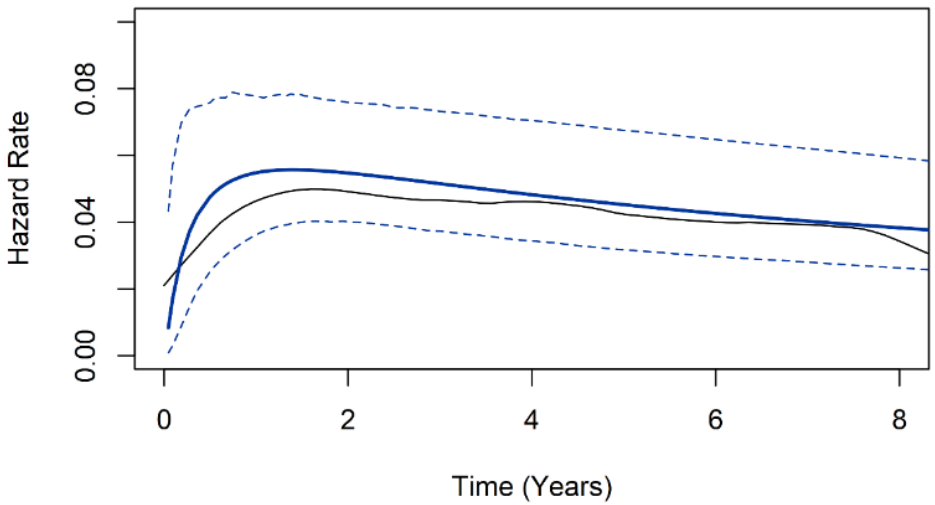
Clinical experts

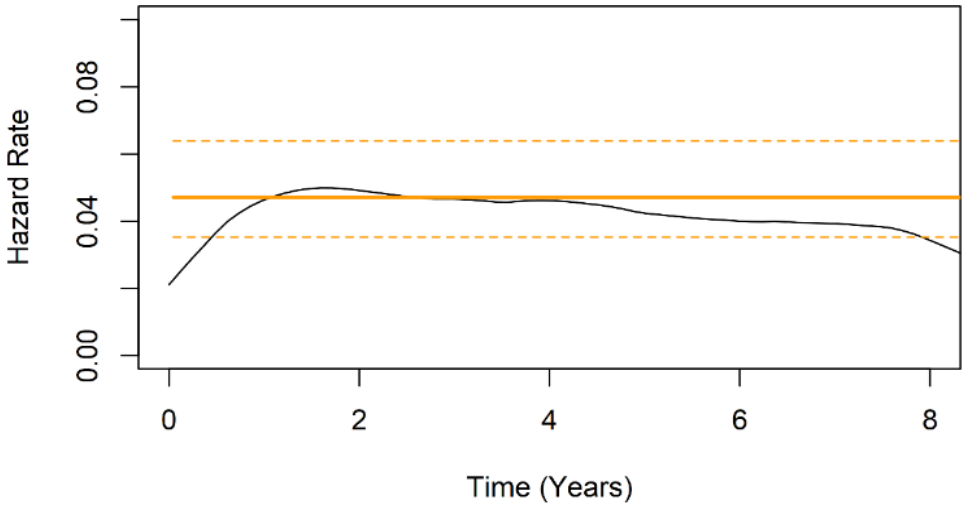
- People with SBS have near normal life expectancy once weaned off PS
- Increased mortality occurs due to lack of monitoring/management of micronutrient deficiencies, intestinal bacterial overgrowth and D-lactic acidosis, and increased incidence of renal calculi

Abbreviations: CKD: chronic kidney disease; IFALD: intestinal failure associated liver disease; ONS: Office of National Statistics; PS: parenteral support

4. Modelling overall survival in adults (2)

Company presented hazard functions predicted by log normal (blue) and exponential (orange) extrapolations compared to Salazar 2021 data (black)





Parametric model	AIC	BIC
Exponential (ERG scenario)	334.48	337.86
Weibull	336.30	343.07
Gompertz	336.42	343.19
Log-normal (company + ERG)	334.62	341.39
Log-logistic	335.47	342.23
Generalised gamma	336.58	346.73

Q. Which survival extrapolation is most appropriate?

NICE

Source: Company response to technical engagement, figure 1; company submission, table 28

5. Modelling of complications - Intestinal failure related liver disease (IFALD) and chronic kidney disease (CKD)

Company

- IFALD (of different levels of severity) and CKD modelled as expected cumulative proportions by PS health state - risk of developing these is assumed to increase with higher PS frequency
  - Based on elicitation of expert opinion
- Teduglutide reduces the incidence of these complications by reducing PS frequency
- Did not model a mortality risk for IFALD and CKD:
  - Clinical feedback states deaths due to IFALD and CKD in people with SBS-IF are very rare
  - Real world data was used to inform mortality – already includes deaths from complications; separately modelling mortality for IFALD and CKD would introduce double counting

ERG

- Lack of structural link in model between proportions surviving with complications and risk of death may lead to overestimation of IFALD/CKD over time causing bias:
  - Overestimated costs + utility losses related to living with IFALD/CKD (bias favours teduglutide)
  - Failure to capture small expected survival benefit for teduglutide (bias against teduglutide)
- Explored scenario excluding IFALD/CKD

Clinical experts

- Teduglutide should reduce risk of IFALD as it reduces PS dependency
- It should also reduce risk of CKD since intestinal fluid absorption improves on treatment
  - Lowered risk of dehydration and secondary renal failure

Q: Is the company's approach to modelling IFALD and CKD appropriate?

Abbreviations: CKD: chronic kidney disease; IFALD: intestinal failure associated liver disease; PS: parenteral support

6. Modelling of adverse events (AEs)

Company

- Used data from STEPS and STEPS-2 for treatment emergent AEs occurring in ≥5% of people
- For teduglutide group, modelled 2 time periods, firstly capturing events in STEPS (6 months) then capturing events in STEPS-2 (post-6-month) – ensures accurate reflection of AE rates over time
- For the standard care group, same approach was used for the first 6 month period using the AEs from placebo group of STEPS. No further evidence available to inform AEs on standard care beyond this, so assumed the event rate remains constant
- Reasonable to expect AEs with teduglutide decrease over time – tolerance likely to improve
- Safety profile of teduglutide after 6 months is more favourable than standard care

ERG

- Satisfied with company's approach to calculating AE rates
- No standard care safety data beyond 6 months – remaining area of uncertainty
  - Comparative data for standard care following the 6-month blinded phase of STEPS may have also shown a reduction in AEs
- Explored the uncertainty in scenarios

Clinical experts

- Would expect decrease in rate of AEs over time with teduglutide; more favourable than standard care in the long term, but only for people with reductions in PS dependency after teduglutide
  - Reduction of PS by even one or two nights swap overnight infusions with daily intramuscular injection; safety is much greater than central venous infusion

Q: Is it reasonable to assume adverse event rates for teduglutide diminish over time and are more favourable than standard care?

Abbreviations: AE: adverse event; PS: parenteral support; SoC: standard care

7. Health state costs – line sepsis by frequency of PS

Company

- Health state costs increase with the number of days PS is required
- Base case assumes 3 to 4 specialist visits regardless of PS independence
- Incidence of line sepsis assumed to increase with increasing frequency of PS
  - In literature, time spent on catheter recognised as being linked to sepsis incidence
  - Days per week of PS is equivalent to catheter days, therefore appropriate to vary rates of line sepsis by days per week of PS in model

ERG

- Model missing situations in which child is admitted to hospital for 48hrs when fever develops as possible catheter-related bloodstream infection (CRBSI); inclusion of such costs would favour teduglutide
- ERG's understanding of catheter days is number of days inserted for access, not number of days used for PS over time
- Supports biological plausibility of relationship between sepsis and increasing frequency of PS, but consider scenario where line sepsis risk is constant across PS states

Clinical experts

- Would expect people with PS independence to require less gastroenterology support
  - No longer require multi-professional specialist visits, care is delivered via outpatients
- No need for central venous catheter, therefore related complications are reduced
- Would expect risk of sepsis to be higher when PS is administered more frequently

Q: Does the incidence of line sepsis increase with the number of days on PS?

Abbreviations: CRBSI: catheter-related bloodstream infection; PS: parenteral support

Key cost effectiveness issues

Cost of home parenteral nutrition has greatest effect on ICER

Issue		Description / key questions	Impact on the ICER
1. ICER for children vs adults		Cost effectiveness for children is much more favourable than for adults: what are the reasons for this?	N/A
2. costs + resource use: HPN + associated medicines	**a**	What is the most appropriate price to use for HPN? • Large differences in the prices by provider • **Major impact on the ICER** • Ranging from cost saving to >£40,000/QALY* • Prices are confidential – full impact seen in Part 2 only	
	b	Associated medicines • What are the most appropriate dosing and administration assumptions for PPIs and antimotility agents in adults and children, including those who are PS independent? • Are they given orally or intravenously? • What are the most appropriate dosing and administration assumptions for ondansentron, fragmin and Taurolock in adults and children?	

Key:
Model driver; Unknown impact; Small/moderate impact

NICE

Abbreviations: HPN, home parenteral nutrition; PPI, proton pump inhibitor, * ERG base case. HPN cost includes delivery and nursing costs

Other cost effectiveness issues

Issue	Description / key questions	Impact on the ICER
3. Health state utility by frequency of PS	Are the company's utilities representative of quality of life for people who have reduced the number of days on PS?	
4. Modelling of overall survival in adults	Are the survival extrapolations plausible and appropriate?	
5. Modelling of complications (IFALD and CKD)	Is the company's approach to modelling IFALD and CKD appropriate?	
6. Modelling of adverse events	Is it reasonable to assume adverse event rates diminish over time and improve over standard care?	
7. Costs related to line sepsis	Does the incidence of line sepsis increase with the number of days on PS?	

Key:
 Model driver;  Unknown impact;  Small/moderate impact

Abbreviations: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; PS, parenteral support.

Innovation and Equality

Innovation

- **Company**
  - Teduglutide is first and only pharmacological treatment approved to treat SBS-IF in UK.
  - Existing therapies for SBS-IF only manage the symptoms of the disease.
  - Teduglutide may enhance intestinal adaptation, improve absorptive capacity of intestine, increase nutrient absorption and enable patients to reduce reliance on PS.
- **ERG**
  - "The economic case hinges on an evidence base with many uncertainties which cannot easily be resolved given the rarity and heterogeneity of SBS-IF“

Equality issues:

- Use of teduglutide not expected to raise any equality issues.

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts